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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/202,805	05/07/99	WAGNER R	4-20921/APCT

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EXAMINER	
DI NOLA BARON,L	
ART UNIT	**PAPER NUMBER**
1615	7

DATE MAILED: 02/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/202,805	Applicant(s) WAGNER ET AL.	
	Examiner Liliana Di Nola-Baron	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *20 July 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

The examiner acknowledges the receipt of the Information Disclosure Statement and the Preliminary Amendment.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment adding claim 28, in which a method of treating headache or chronic heart failure is claimed, represents a departure from the specification (See p.8) and the claims as originally filed and the applicant has not pointed out where the support comes from.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. in view of Makino et al. The claimed invention relates to solid oral pharmaceutical compositions

containing valsartan and their preparation by compression method. Muller et al. discloses a method of treating male patients with single oral doses of valsartan as an antihypertensive drug (See e.g., p.232). Muller et al. does not disclose the method of preparation of the oral doses of valsartan. Makino et al. describes a method of producing a fast dissolving tablet by compression-molding a composition comprising a pharmacologically active ingredient (See e.g., col.3, lines 3-7). Makino et al. teaches that the active ingredient can be an antihypertensive drug (See e.g., col.3, lines 35-46). Additionally, Makino et al. discloses that the composition may contain a variety of additives which are commonly employed in the manufacture of tablets (See e.g., col. 5, lines 51-54). Makino et al. also teaches that the recommendable proportion of the active ingredient in the composition is generally about 0.05 to 90% by weight and preferably 0.1 to 70% and more preferably 0.3 to 60% by weight (See e.g., col.4, lines 56-60). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to synthesize a solid oral dosage pharmaceutical composition of valsartan using the compression-molding methods described by Makino et al. One of ordinary skill in the art would have been motivated to synthesize the pharmaceutical composition of valsartan and additives by compression methods to increase the proportion by weight of the active ingredient and achieve a faster disintegration rate of the oral preparation. One of ordinary skill in the art would have expected this preparation to be successful, since the method described by Makino et al. relates to pharmacologically active ingredients, including antihypertensive drugs. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

4. Claims 4-17, 25 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. in view of Makino et al as applied to claims 1-3 above, and further in view of dePadova, Fujimura et al., Armah et al., Ku et al and Dopper et al. The claimed inventions relate to solid oral pharmaceutical preparations produced by compression methods, wherein the active agent consists entirely of valsartan or a pharmaceutically acceptable salt thereof, or the active agent consists of a combination of valsartan or a pharmaceutically acceptable salt thereof and hydrochlorothiazide. dePadova describes a method of treating patients with premenstrual tension syndrome with oral doses of AT1 receptor antagonists and salts thereof (See e.g., col. 4, lines 54-61 and col. 5, lines 1-64). dePadova teaches that the dose of the AT1 antagonist may vary from patient to patient (See e.g., col. 6, line 1) and discloses an oral dosage ranging from about 0.5 mg. to about 500 mg. over a period of substantially twenty-four hours (See e.g., col. 6, lines 24-27). De Padova does not mention valsartan in the invention. Muller et al. characterizes valsartan as an orally active, potent and specific competitive Ang II antagonist acting at the AT1 receptor subtype, used as antihypertensive drug (See e.g., p. 232). Additionally, Muller et al. describes a method of treating male subjects with single, oral doses of 40 mg and 80 mg of valsartan. Fujimura et al. describes a method of treating hypertensive rats with a single p.o. administration of valsartan only and in combination with thiazide and nifedipine. Fujimura et al. discloses administering valsartan at a dosage of 3 mg./kg. (See e.g., abstract). Armah et al. discloses pharmaceutical composition containing the antihypertensive drug moxonidine or its pharmaceutically acceptable salts and hydrochlorothiazide for the treatment of hypertension (See e.g., col.1, lines 26-48). Armah et al. teaches that the daily dose of the active substances

administered orally can include 12.5 to 100 mg of hydrochlorothiazide (See e.g., col.2, lines 24-28) and in particular 12.5 or 25 mg of hydrochlorothiazide (See e.g., col.2, line17). Additionally, Armah et al. discloses that the pharmaceutical compositions can be solid or liquid and in the pharmaceutical forms customarily used in human medicine, such as tablets or sugar-coated tablets (See e.g., col.3, lines 54-61). Armah et al. does not include valsartan in the disclosed pharmaceutical compositions. Ku et al. discloses pharmaceutical compositions of irbesartan, containing as active ingredients irbesartan alone or in combination with a diuretic such as hydrochlorothiazide (See e.g., col.1, lines 38-41) Ku et al. characterizes irbesartan as a potent, long-acting angiotensin II receptor antagonist which is particularly useful in the treatment of cardiovascular ailments such as hypertension and heart failure (See e.g., col.1, lines 19-23). Ku et al. teaches that the pharmaceutical compositions containing irbesartan may be used to treat or prevent disorders, including cardiovascular disorders, venous insufficiency, glaucoma, diabetic retinopathy, renal insufficiency and various complains of the central nervous system (See e.g., col.7, lines 17-23). Ku et al. discloses that tablets prepared from the compositions preferably contain from about 25 to about 300 mg of irbesartan, most preferably from about 75 to 300 mg of irbesartan (See e.g., col.7, lines 5-8). Ku et al. describes pharmaceutical compositions of irbesartan, especially suitable for forming tablets, in which microcrystalline cellulose may be employed as diluent or disintegrant in the range of 5-15% (See e.g., col. 3, lines 33-41 and col.4, lines 1-10). Dopper et al. discloses pharmaceutical compositions including a disintegrating agent, such as cross-linked PVP. Dopper et al. teaches that the disintegrators will typically make up from 5 to 50%, preferably 5 to 15%, by weight of the resulting granules (See e.g., col.3, lines 13-

21). The teachings of Makino et al. are summarized above (See rejection to claims 1-3). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to synthesize a solid oral composition, possibly in form of tablet or sugar-coated tablet, using the method described by Makino et al., wherein the active agent consists entirely of valsartan in the dosage range disclosed by dePadova or at the concentration taught by Muller et al., or alternatively to synthesize a solid oral composition using the method described by Makino et al., wherein the active agent consists of a combination of valsartan and hydrochlorothiazide in the ratio disclosed by Fujimura et al. and suggested by Armah et al. and Ku et al. and comprising microcrystalline cellulose and/or cross-linked PVP as additives. One having ordinary skill in the art would have been motivated to synthesize such pharmaceutical preparations to produce small, easily swallowed and highly efficient tablets in large scale, achieve a faster disintegration rate of the oral preparation and optimize the dosage of valsartan for an effective treatment of disorders, such as those described by Ku et al. Because of the teachings of Muller et al. that the hypertensive drug valsartan is an AT1 receptor antagonist, one having ordinary skill in the art would have a reasonable expectation that pharmaceutical compositions of valsartan at an oral dosage range disclosed by dePadova or in combination with hydrochlorothiazide, as described by Ku et al. and Armah et al. would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

5. Claims 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., Makino et al, dePadova, Fujimura et al., Armah et al., Ku et al and Dopper et al. as applied to

claims 4-17 and 25 above, and further in view of Lachman et al. and Tamas et al. The claimed inventions relate to a process of forming solid oral compositions of valsartan and hydrochlorothiazide comprising compression granulation. Ku et al. describes a method for the preparation of pharmaceutical compositions containing irbesartan comprising a granulation process, followed by sizing, mixing the additives and compression to form tablets (See e.g., col.6, lines 27-64). Ku et al. teaches that sizing the blend to break up aggregates after mixing the irbesartan, diuretic and additives is optional (See e.g., col. 6, lines 33-42). Ku et al. characterizes irbesartan as a potent, long-acting angiotensin II receptor antagonist which is particularly useful in the treatment of cardiovascular ailments such as hypertension and heart failure (See e.g., col.1, lines 19-23). Ku et al. does not include valsartan in the disclosed pharmaceutical compositions. Muller et al. characterizes valsartan as an orally active, potent and specific competitive Ang II antagonist acting at the AT1 receptor subtype, used as antihypertensive drug (See e.g., p. 232). Lachman et al. teaches that compression granulation may involve the process of slugging, followed by screening (See e.g., p.318-319). In addition, Lachman et al. teaches that on a large scale compression granulation can be performed on a roller compactor (See e.g., p. 319). Tamas et al. discloses a process for preparation of sustained release solid pharmaceutical compositions (See e.g., abstract). Tamas et al. teaches that powder mixtures can be pressed into tablets under a pressure of 100-120kN. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to synthesize a solid oral composition of valsartan, hydrochlorothiazide and additives as disclosed by dePadova, Fujimura et al., Armah et al., Ku et al and Dopper et al. and modify the method described by Makino et al. in view of the teachings

of Ku et al. and Tamas et al. One having ordinary skill in the art would have been motivated to synthesize such pharmaceutical preparations and modify its method of preparation to produce in large-scale tablets with fast disintegration rate and desirable physical properties. Because of the teachings of Muller et al. that the hypertensive drug valsartan is an AT1 receptor antagonist, one having ordinary skill in the art would have a reasonable expectation that the method described by Ku et al. for pharmaceutical compositions containing irbesartan would be successfully applicable to pharmaceutical compositions containing valsartan. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Friday from 6:30AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

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